

January 6, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852



[Docket No. 00D-0186] International Conference on Harmonization; Guidance on M4 Common Technical Document; REFERENCE: M4E: CTD - Efficacy

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's research has produced many of the most important pharmaceutical products on the market today.

Merck has participated with health authorities and industry scientists from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). Merck continues to support the objectives of ICH: to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical and biological products caused by incompatible regulatory schemes.

In the course of bringing Merck's product candidates through developmental testing and clinical trials to the market, Merck has filed numerous original and supplemental New Drug Applications (NDAs) and Biological License Applications (BLAs). Merck typically prepares a single Worldwide Marketing Application (WMA) which is filed electronically and, less often, filed on paper, in most countries in the world, simultaneously. Therefore, we are very interested in this *ICH Guidance on M4 Common Technical Document* and well qualified to comment on it.

Although all ICH participants have valiantly pursued harmonization of documentation for marketing applications, this FDA version of the M4 Common Technical Document (CTD), specifically the *M4E: CTD - Efficacy* guidance differs from the European *Notice To Applicant's* with regard to the same information, in a way that is fairly significant. Indeed, this one instance of *lack* of harmonization is precisely an example of regional distinctions that have been considered unjustified and unnecessary and, therefore, eliminated during the ICH process.

The numbering/indexing systems used by the US FDA and by the European authorities, when more than one indication is submitted for a single product in one marketing application, are not harmonized and will require regional manipulation that should not be necessary.

FDA's Guidance for Industry M4E: CTD -- Efficacy, Module 2 - Section 2.7.3 Summary of Clinical Efficacy (page 22) reads:

"A separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labeled by indication (e.g., 2.7.3 pneumonia, 2.7.3 URI)".

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In contrast, the European *Notice to Applicants (NTA)* provides the following instructions for the same information in Module 2 - Section 2.7.3 Summary of Clinical Efficacy (page 139 of 165):


"A separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labeled 2.7.3A, 2.7.3B, 2.7.3C".

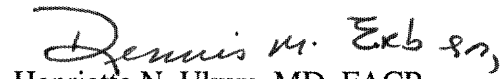
As noted above, Merck, as many other global companies, prepares one Worldwide Marketing Application (WMA) to file simultaneously in many countries. This difference in the numbering systems between the US and Europe will require that one WMA be created for filing in one geographic area, then, altered for filing in the other region, thereby prohibiting simultaneous filings. This unique numbering system will equally affect both paper filings and electronic.

This difference in numbering systems is not included in Module 1 where regional distinctions are noted, and rightly so. At the same time, we understand that other numbering and indexing systems have been harmonized to avoid similar problems. Therefore, we must conclude that this difference is an oversight and we bring it to your attention in the interest of clarity and cooperation.

We welcome the opportunity to provide feedback on *ICH Guidance on M4 Common Technical Document* and, if appropriate, we would be pleased to meet with you to discuss this issue.

Sincerely,


Bonnie J. Goldmann, MD
Vice President
Regulatory Affairs-US


Henrietta N. Ukwu, MD, FACP
Vice President
Worldwide Regulatory Affairs
Vaccines/Biologics

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